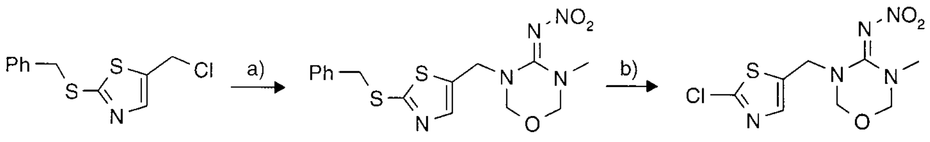

Figure 4. Alternative synthesis of CGA 293'343 from the intermediate **12**. Reaction conditions: a) oxadiazinane **1**, DMF, K_2CO_3, 2 h, 60°C, 75%, b) HCl, H_2O, C_6H_5Cl, Cl_2, 6 h, 80%.

ated to give **2**. Another synthetic approach to **12** is chlorination of 2-benzylmercapto-5-methylene-thiazoline **11**,[14] which is available by alkylation of **8** with benzylbromide. **12** was also prepared by treatment of diol **17** with $SOCl_2$.[13] Diol **17** was constructed from the previously described dithiocarbamate **16** by reaction with glycidyl aldehyde.[15]

An alternative synthesis is shown in Fig 4. Coupling of **12** with **1** followed by chlorination of the intermediate **18** gave CGA 293'343.[13]

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Non-steroidal ecdysone agonists: New tools for IPM and insect resistance management

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Abstract: The non-steroidal, bis-acylhydrazine agonists of the insect molting hormone, 20-hydroxyecdysone, were first discovered over ten years ago. An extensive structure–activity optimization program yielded one commercial insecticide, tebufenozide (RH-5992) and two additional candidate insecticides (methoxyfenozide and halofenozide) which are in development. Tebufenozide is highly selective for lepidopteran pest control and is thus useful for IPM and resistance management programs. Methoxyfenozide (RH-2485) is also lepidopteran-selective but significantly more potent than tebufenozide and offers control of a wider range of lepidopteran pests. Halofenozide (RH-0345) is generally less potent and selective than tebufenozide or methoxyfenozide. However, its physical and biological properties make it well suited for control of beetle grubs and caterpillars in the soil. Target pest selectivity, new and novel mode of action, ecotoxicological safety and safety to beneficial arthropods make these insecticides valuable tools for integrated pest and resistance management programs.

Keywords: tebufenozide; methoxyfenozide; halofenozide; ecdysone agonists; RH-5992; RH-2485; RH-0345; IPM; resistance management programs

The steroid insect moulting hormone, 20-hydroxyecdysone (20E), and the sesquiterpenoid juvenile hormone play a central role in the regulation of the growth and development, as well as of reproductive processes, in insects. As such, chemicals which mimic or antagonize the action of these two hormones have been sought for use as safe, third-generation pesticides. While success in the discovery of juvenile hormone mimetics came much earlier,[1] it is only recently that insecticides which act as agonists of 20E have been discovered.[2]

Scientists at Rohm and Haas Company have discovered three non-steroidal ecdysone agonists, all of which belong to bis-acylhydrazine chemistry.[2] One of these, *N-tert*-butyl-*N'*-(4-ethylbenzoyl)-3,5-dimethylbenzohydrazide (tebufenozide; RH5992) was the first to be commercialized as a leptidopteran-specific insecticide under the trade names Mimic®, Confirm® and Romdan® in several countries.

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More recently, two other insecticides with similar chemistry have been discovered: *N-tert*-butyl-*N'*-(2-methyl-3-methoxybenzoyl)-3,5-dimethylbenzohydrazide (RH-2485) and *N-tert*-butyl-*N'*-(4-chlorobenzoyl)benzohydrazide (RH0345), proposed common names methoxyfenozide and halofenozide respectively. Halofenozide is under development by RohMid (a joint venture between Rohm and Haas Company and American Cyanamid) under the commercial name, Mach 2® for the turf market in the USA.

The mode of action of the non-steroidal ecdysone agonists has been well documented;[2] they manifest their biological activity via interaction with the ecdysone receptor complex. The action of 20E is also mediated through interaction with the ecdysone receptor complex, which consist of a heterodimeric complex of the ecdysone receptor and ultraspiracle protein[3] and other associated proteins, whose function is not fully understood.[4] In spite of the ecdysone mode of action of the bis-acylhydrazines, and the fact that almost all insects use 20E as the insect molting hormone, at least two of the non-steroidal insecticides (tebufenozide and methoxyfenozide) are selectively toxic to lepidopteran pests. This target-pest selective toxicity does not appear to be due to differences in the transport or metabolism of the agonists in susceptible and non-susceptible insects (Ref 5, and Dhadialla TS and Smagghe G, unpublished). However, ligand binding studies with ecdysone receptor extracts of tissues or cells from susceptible and non-susceptible insects demonstrate that the activity of tebufenozide and methoxyfenozide is directly correlated with their binding affinity to an ecdysone receptor complex.[2,5]

Halofenozide, which is active against coleopteran larvae, and to a much lesser extent against lepidopteran larvae than either tebufenozide or methoxyfenozide, binds to the ecdysone receptor complexes from susceptible insects with much lower affinity than does tebufenozide.[2] Preliminary data suggest that halofenozide may overcome its weaker binding affinity to the coleopteran receptor by having greater metabolic stability than the other two ecdysone agonists (Dhadialla TS and Taddei MG, unpublished).

All the three ecdysone agonists induce premature lethal molts in intoxicated larvae which have double cuticles. However, the new cuticle has an abnormal endocuticle structure (Ref 6, and Dhadialla TS, Trader C and Taddei MG, unpublished).

Both tebufenozide and methoxyfenozide are potent against a broad range of lepidopteran pests, except that methoxyfenozide is 3- to 10-fold more potent than tebufenozide and has a broader spectrum of activity amonst lepidoptera, so that methoxyfenozide is being developed more widely than tebufenozide. Halofenozide is markedly less active against most lepidopteran pests, but is considerably more active against beetles and is being developed for the control of grub and lepidopteran pests in the turf market.[2]

Excellent efficacy of these compounds has been demonstrated globally in a variety of food crops, turf and ornamentals.[7,8] Rates of tebufenozide and methoxyfenozide for controlling lepidopterous pests vary widely from crop to crop and from region to region. For example, tebufenozide is currently applied at rates as low as 30 g AI ha^{-1} for control of *Anticarsia gemmatalis* (Hübn) on soybean in Brazil to as much as 450–600 g AI ha^{-1} for control of *Spodoptera exigua* Hübn on vegetables in Thailand. In general, use rates for methoxyfenozide are around one-half of those applied for tebufenozide on most crops.

The non-steroidal ecdysone agonist insecticides exhibit remarkable ecotoxicological safety. All three bis-acylhdrazines have low acute toxicity to mammals, birds and fish. They are non-mutagenic and non-toxic in developmental and reproductive studies. There is substantial data on the safety of tebufenozide to predacious mites, spiders, wasps, lacewings, beetles, true bugs and dragonflies, as well as bees. Methoxyfenozide is also safe to honey bees as well as to several predatory mites and hymenopterous parasitoids. Due to their selective activity against target pests and safety to beneficial parasitoid and predatory insects, these insecticides are ideally suited for integrated pest management programs.[2]

Although it is inevitable that insects will develop resistance or cross-resistance to any new insecticide, it is unlikely that there will be target site cross-resistance for the bis-acylhydrazine insecticides with other known insecticides due to their very different mode of action. No cross-resistance was found between cartap and tebufenozide in rice stem borer, *Chilo suppressalis* Walk,[9] between methomyl and tebufenozide in tea tortrix, *Homona magnamima* Diak,[8] nor between azinphos-methyl and diflubenzuron and tebufenozide in organophosphorus-resistant populations of tufted apple bud moth, *Platynota idaeusalis* Walk.[10] Selection of an organophosphate-resistant strain of green-headed leafroller, *Planotortrix octa* Dugdale, with either azinphosmethyl or tebufenozide in the laboratory resulted in an increased tolerance for both compounds.[11] Loss of efficacy of tebufenozide was observed in laboratory strains of codling moth, *Cydia pomonella* L, made resistant to diflubenzuron.[12] However, despite these laboratory studies, numerous internal studies conducted at Rohm and Haas Company have revealed no cross-resistance between either tebufenozide and/or methoxyfenozide and other insecticide chemistries, eg between: (1) diflubenzuron and tebufenozide in diflubenzuron-resistant *C pomonella*;[13] (2) methoxyfenozide, pyrethroids, and a carbamate in pyrethroid-resistant populations of tobacco budworm, *Heliothis virescens* F; (3) azinphos-methyl and tebufenozide in azinophos-methyl-resistant *C pomonella*; (4) chlorofluazuron and tebufenozide in chlorfluazuron-resistant strains of beet armyworm,

S exigua; (5) chlorfluazuron and tebufenozide and methoxyfenozide in chlorfluazuron-resistant strains of tea tortrix, *H magnamima*; and (6) flufenoxuron and tebufenozide in flufenoxuron-resistant strains of *S exigua and C pomonella*. Attempts to select *S exigua* resistant to tebufenozide in the laboratory have so far been unsuccessful. Adults developing from larvae maintained over 12 generations at LC_{25} levels of tebufenozide had complete loss of fecundity.[14]

Rohm and Haas Company has developed a pro-active platform to manage resistance to ecdysone agonist insecticides. Global resistance monitoring programs are currently underway on *C pomonella*, *S exigua*, *H mamnamima*, certain Heliothine pests, and certain leafroller species to establish baseline susceptibility data as well to detect any shifts in susceptibility over time. In addition, we pro-actively advocate the use of traditional approaches for managing insecticide resistance, including frequent and repeated rotation with other insecticides with different modes of action to minimize selection pressure, limitations on the number and sequences of applications on certain crops, and incorporation of integrated pest management methods to reduce pesticide use and prolong these products in the marketplace.

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Synthesis and insecticidal activity of 3-aminoquinazolinone derivatives

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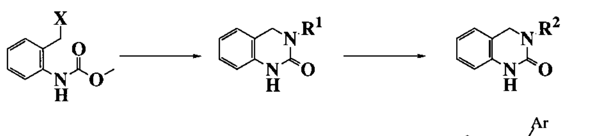
Abstract: The discovery, structure–activity relationships and insecticidal properties of R-768 (1-propionyl-3-(3-pyridylmethylamino)-1,2,3,4-tetrahydroquinazolin- 2-one) and related compounds are described.

Keywords: 3-aminoquinazalones; R-768; insecticide; aphicide

In the course of research on methoxyacrylate fungicides, it was found that compounds having a carbamate group instead of a methoxyacrylate group in the relevant compounds also showed fungicidal activity against a broad spectrum of fungi.[1] Structural modification of those compounds was conducted to find a more active compound.[2] In the synthetic process, 2-halomethylphenyl carbamates (Fig 1; **1**) were used as one of the starting materials.[3] These proved to be interesting intermediates for synthesizing heterocycles, because they have two different electrophilic functional groups which can react with a primary amine at the 1,1-position of the



1 X = halogen

2a $R^1 = CH_3$
2b $= NH_2$
2c $= OH$

3a $R^2 = N{=}$ Ar
3b $= NHCOR^3$
3c $= NHCONHR^3$
(Ar = 3-pyridyl)
(R^3 = alkyl, phenyl etc)

Figure 1. Synthesis of 3-substituted quinazolinones.

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